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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FUBARA, BLESSING M	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
03/23/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com

Office Action Summary	Application No.	Applicant(s)	
	09/981,020	KOHANE ET AL.	
	Examiner	Art Unit	
	BLESSING M. FUBARA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/12/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-15,17-20,23-25,27,30,37,47,58-65,80,84,86-91 and 96-107* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-15,17-20,23-25,27,30,37,47,58-65,80,84,86-91 and 96-107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

The examiner acknowledges receipt of request for extension of time, notice of appeal, pre-brief conference request and remarks, all filed 12/12/08. Claims 1, 7-15, 17-20, 23-25, 27, 30, 37, 47, 58-65, 80, 84, 86-91 and 96-107 are pending.

Previous rejections that are not reiterated herein are withdrawn.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 7-15, 17-20, 23-25, 27, 30, 37, 47, 58-65, 80, 84, 86-91 and 96-107 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is new matter

rejection. The original specification does not envision microparticle composition that is not a liposome or does not comprise synthetic polymer. Applicant, for example, studied biocompatibility of particles in terms of inflammatory response and gross neural injury and mentions Yanez et al. and "touch evoked agitation" as it relates to injections of liposomes (paragraphs [0139] and [0152] of the published application). The specification as originally filed does not envision microparticles and compositions that are free of synthetic polymers that cover the broad scope of synthetic polymer. For example paragraph [0042] of the published application describes the lipid-protein-sugar-particles to optionally contain PLGA, PGA, polyesters, polyanhydrides or polyamides and these are not the only synthetic polymers.

Response to Arguments

5. Applicant's arguments filed 12/12/08 have been fully considered but they are not persuasive.

6. Applicant insists that the specification describes particles that do not include synthetic polymer citing pages 3, 14 and 52 of the specification showing microparticles in which none of the components is a synthetic polymer or liposome. Furthermore applicant reiterates the arguments presented in the personal interview of Feb. 4, 2008 that none of the methods in the specification can be used to produce liposmes. Applicant concludes that the specification describes solid microparticles that are not liposomes. The examiner respectfully disagrees because the mere absence of positive recitation in the disclosure is not the basis for exclusion (see In re Grasselli and Ex parte Grasselli).

7. Claims 1, 7-15, 17-20, 23-25, 27, 30, 37, 47, 58-65, 80, 84, 86-91 and 96-107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. The claims recite derivatives of cellulose and dextran. The boundaries of the derivatives of cellulose and dextran are not clear.

9. It is suggested that the term "derivatives" be removed from the claims in order to overcome the rejection.

10. The claims also claim proteins by their sources and it is unclear what these proteins are. Applicant is seeking protection for composition or matrix that contains commercially available proteins, proteins that are purified from natural sources, recombinant proteins and proteins that are chemically synthesized. It is unclear what these proteins are. There is no definite proteins claimed by claiming the sources and even the source such as natural sources is boundless.

Response to Arguments

11. Applicant's arguments filed 12/12/08 have been fully considered but they are not persuasive.

12. Applicant argues that the meaning of derivatives of cellulose and dextran is well understood and that the search of the USPTO's data base reveals 34,204 issued patents that recite cellulose derivative. In response, it is noted that while that may be so, each application for patent is fully examined on its merit. Secondly, while the meaning of derivatives of cellulose and dextran may be understood, the boundaries of these derivatives for the protection sought are not defined. What are the cellulose derivatives that applicant is seeking protection? And what are the dextran derivatives that the applicant is seeking protection? The specification does not

say that by derivatives of dextran, we mean .... or derivatives of dextran are .... Really, the boundaries for the derivatives of dextran and cellulose are not defined. Applicant can claim what the derivatives of dextran and cellulose are using a Markush type language to capture the boundaries of these derivatives making sure that the original specification as filed supports these limitations.

13. Claims 1, 7-15, 17-20, 23-25, 27, 30, 37, 47, 58-65, 80, 84, 86-91 and 96-107 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is written description.

14. The specification does not describe what proteins meet the limitation of "commercially available proteins," proteins that are purified from natural sources, "recombinant proteins" and proteins that are chemically synthesized proteins. The specification has not identified at least one protein that is recombinant, commercially available, chemically synthesized or purified from natural sources and what the natural source may be.

15.

Specification

16. The disclosure remains objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see paragraph [0011] of the published application, for

example). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Please note that applicant did not correct the specification regarding this objection and applicant did not provide any arguments against the request for consideration. However, hyperlinks and/or browser executable code are not permitted in the specification according to MPEP § 608.01.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 1, 7, 12-15, 17-20, 23-25, 27, 30, 37, 47, 58-65, 80, 84, 86-91 and 96-99, 101, 103-107 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein et al. (US 6,423,345).

20. Bernstein discloses a microparticulate matrix comprising hydrophobic compounds and polymer matrix (column 2, lines 15-20); the microparticles have diameter that is dependent on the intended route of administration, for example, for intravascular administration, the diameter between 0.5 and 8 microns; between 1 and 100 micron for subcutaneous or intramuscular administration; and between 0.5 and 5mm for oral administration (column 2, lines 22-29). The hydrophobic compounds are lipids such as phospholipids, most preferably dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), diarachidoylphosphatidylcholine (DAPC), dibehenoylphosphatidylcholine (DBPC), ditricosanoylphosphatidylcholine (DTPC), and dilignoceroylphatidylcholine (DLPC) (column 2, lines 38-46), and the lipids are present a ratio of 0.01-60 weight lipid to the weight of the polymer, and most preferred at 0.1-30 weight lipid to weight polymer. Active agents such as therapeutic agents, prophylactic agents, proteins, peptides, sugars, oligosaccharide, nucleic acid and other natural agents are incorporated into the matrix for delivery (Column 6, line 56 to column 7, line 5). Bernstein teaches that the matrix includes one or more materials in which the drug is dispersed, entrapped or encapsulated (column 3, lines 15-17). The matrix material is synthetic or natural polymer (column 3, lines 36, 37) and it is specifically stated that natural polymers have equivalent or better properties such as hydrolytic degradation (column 3, lines 39, 40); Bernstein also discloses that the polymer is selected based on the time required for in vivo stability in terms of the time required for distribution to the site where delivery is desired

(column 3, lines 41-44). The natural polymers, one or more of which can be used as suggested by column 3, line 16, are proteins such as albumin and prolamines such as zein, and polysaccharides such as alginate and cellulose (column 4, lines 19-22). Thus when the matrix composition is made up of one or more natural polymers such as albumin and polysaccharides, and the lipid and active agents as described above, then composition of claim 1, 86, 101, 104 and the method claims 62 and 103 are met except for the amounts of protein and the sugar, which is the polysaccharide. Therefore, taking the teaching of Bernstein, one having ordinary skill in the art at the time the invention was made would have reasonable expectation that, following the suggestion to use one or more polymer for the matrix and motivated by the teaching that natural polymers may have better properties to distribute the drug to the target delivery site, combination of one or more natural polymers and lipid in appropriate amounts would produce delivery vehicle that would degrade by hydrolysis and distribute the active agent to the target delivery site. The amounts recited in the claims are not inventive over Bernstein absent factual evidence.

21. The active agents listed in Bernstein meets the generic therapeutic agent of claim 7; the vasodilators (column 6, line 65) meet claim 12; the therapeutic or prophylactic agent (column 6, line 58) meets claim 17; the lipids in Bernstein meet claims 18-20, 24, 25, 27, 97, 98 also when the active agent is nucleic acid, 99. When the natural protein is albumin, claims 30, 88, 106 are met. Since Bernstein teaches the same lipids as claim 1, claim 23 defining the lipid to have no charge is met. It is also noted that the matrix microparticles are mixed with pharmaceutically acceptable agents including sugars such as mannitol, sucrose, lactose and trehalose (column 10, lines 9 and 10) meeting claims 1, 37, 62, 86, 89, 101, 103, 104 and 107. The size of the

microparticles as described above meets claims 1, 58-62, 80, 86, 101, 103, 104. Claim 84 is a product by process claim and the product of Bernstein meets the claim.

The agents described in Bernstein are those that may be labeled with a fluorescent label or an enzymatic or chromatographically detectable agents (column 6, lines 61-63) are diagnostic agents. With respect to the amounts of lipid, protein and sugar claimed in claims 48-56 of the instant application, Bernstein teaches that the content of the lipid in the matrix is 0.01-60% in relation to the content of the polymer (column 6, lines 18-21) and the amount of polymer (protein) is 0.1-60% (column 4, lines 62-64). Therefore, the patent contemplates an amount of lipid up to 36%. With respect to the size of the claimed size of the microparticles claimed in claims 57-60 and 80 of the application, Bernstein discloses that the microparticles of the invention are manufactured with a diameter suitable for the intended route of administration, and discloses particles for intravascular administration having a diameter of 0.5 to 8 microns (column 2, lines 20-27). With regard to the particle size claimed in instant claim 61, Bernstein is deficient in the sense that the patent fails to disclose particles smaller than 0.5 microns. Applicant has not established comparable example in the specification to demonstrate that the claimed small size provides some unusual and/or unexpected results. It appears to the examiner that the smaller size of particles does nothing additional to the compositions of the invention, especially in view of the teachings of the prior art, that the microparticles of the invention can be administered by any route, including administration to the lungs (column 9, lines 56-63).

With respect to the method of preparing the microparticles claimed in claim 62, Bernstein discloses that the microparticles of the invention can be produced by spray drying the polymer solution formed by dissolving the polymer (protein) and the lipid in the appropriate

solvent, dispersing the active agent into the polymer solution (column 8, lines 18-33). With regard to the method of administering an agent claimed in claims 63-65 of the application, Bernstein discloses that the microparticles are combined with a pharmaceutically acceptable carrier and administered to a patient by injection into a blood vessel, subcutaneously, intramuscularly or orally (column 9, line 64 to column 10 line 6). Oral administration implies placing the microparticles in the oral cavity of the patient, thus the patent contemplates placing the microparticles in a body cavity of the patient, as claimed in claim 65 of the instant application. With respect to the ratio of lipid to protein to sugar claimed in claim 47 and also to the ratios in claims 92 and 95 of the application, it is noted that applicants have no demonstration that the ratio of lipid claimed in the instant application provides unusual/unexpected results and there is no comparable example in the specification to demonstrate that the claimed ratio of lipid provides some unusual and/or unexpected results. It appears to the examiner that the higher ratio of lipid does nothing additional to the compositions of the invention, especially in view of the teachings of the prior art, that the hydrophobic compound integrated in the polymeric matrix modifies the diffusion of water into the microparticle and the diffusion of solubilized drug out of the matrix (column 2, lines 8-11).

22. Claims 8-11 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein et al. (US 6,423,345) in view of Goldenheim et al. (US 6,534,081).

The teachings of Bernstein et al. have been summarized above. The prior art is deficient in the fact, that it does not specifically include the anesthetics recited in claims 8-10 of the application and anticonvulsant agents, as claimed in claim 11, among the therapeutic agents

encapsulated in the microparticles of the invention. Goldenheim provides sustained release dosage forms comprising a local anesthetic and an augmenting agent, and includes bupivacaine, dibucaine, tetracaine and lidocaine among the preferred local anesthetics used in the invention (column 3, line 50 to column 4, line 51). Goldenheim teaches that the local anesthetic is prepared in matrices of controlled release injectable microspheres (column 5, lines 60-64), and the formulations of the invention are suitable for administration in all body spaces and cavities (column 6, lines 55-59). Goldenheim discloses formulations comprising microparticles comprising a local anesthetic, an augmenting agent and a sustained release polymer selected from synthetic polymers, proteins, polysaccharides and combinations thereof (column 7, lines 20-47) and imaging or diagnostic agents (column 7, lines 7, 8, 44-47; column 9, line 40-44) and the imaging agents meet new claim 102. Thus, the patent provides the general teachings that local anesthetics can be delivered by microparticle compositions and specifically discloses the compounds recited in claims 8-10 of the instant application. With respect to claim 11, Goldenheim includes anticonvulsants among the augmenting agents incorporated in the compositions of the invention (column 12, lines 9-12).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Bernstein and the teachings of Goldenheim with the expectation of producing microparticles for the controlled delivery of local anesthetics and anticonvulsant drugs and imaging agents.

23. Claims 1 and 100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein et al. (US 6,423,345) in view of Compans et al. (US 4,790,987).

Bernstein is described above as disclosing microparticles (column 1, line 18) and the microparticles comprise hydrophobic compounds such a DPPC, a lipid (column 2, lines 38-48), natural polymers such as albumin, a protein (column 4, lines 19 and 20) keeping in mind that column 3, lines 35, 36, 37-42 contemplate that synthetic as well as natural polymer can be used to form the matrix. Also, blends of polymers are contemplated and cellulose in column 4, line 21 meets the limitation of the sugar. The limitation for sugar is further met by the teaching that bulking agents include sugars such as mannitol, sucrose, lactose, fructose and trehalose (column 10, lines 8-11 and column 9, lines 64-66 for carriers). While Bernstein discloses the delivery of active therapeutic and prophylactic agents among the active agents, which are incorporated into the matrix (column 6, line 56 to column 7, line 5), Bernstein does not teach the delivery of vaccines. However, Compans describes the delivery of vaccine in lipid containing matrix (claims 1-3). Therefore, taking the teachings of the prior art, one having ordinary skill in the art at the time the invention was made would have reasonable expectation of success that incorporating vaccine a matrix composition containing lipid, sugar and protein would provide a matrix composition for effective delivery of vaccines.

Response to Arguments

24. Applicant's arguments filed 1212/08 have been fully considered but they are not persuasive.

25. Applicant argues that Bernstein does not teach microparticle that contains a lipid and a protein and a sugar. The examiner disagrees and the examiner did not agree with applicant, rather, the examiner indicated that arguments presented in any response will be considered. Furthermore, it is noted that Bernstein teaches that natural polymer has better properties when it

comes to distributing the active agents to the desired sites in light of the hydrolytic degradation of the natural polymer. Bernstein specifically teaches that one or more matrix materials are used for the matrix. Even if a single natural polymer is used, its is noted that albumin is specifically named and is one of the polymers that can be used and the list contains three, albumin, zein and prolamines. Secondly, Bernstein is clear that bulking agents such as sugars such as mannitol, lactose, fructose, and trehalose are combined with the microparticles (column 10, lines 6-11) so that if for the sake of argument, one or more natural polymers are not employed by using proteins and polysaccharides (column 3, line 16, 38-40; column 4, lines 19-22), Bernstein contemplates combining sugars with the microparticles and when that is done, the matrix will have protein, sugar and lipid. It is also note that the comprising language is open.

26. Applicants arguments regarding Bernstein and PLGA and the examples, it is noted that a prior art reference such as Bernstein is not limited to the examples, but the reference as a whole must be considered for what it teaches. In the instant case, when Bernstein is considered for what it teaches, it will be clear that Bernstein anticipates use of one or more matrix materials and suggests that natural polymers, which are matrix materials, have better properties. Further also, the microparticles containing PLGA in the examples are but an embodiment and that for which the natural polymer would have better properties is another embodiment.

27. Therefore, on the whole, Bernstein contemplates compositions containing, lipid, protein and sugar.

28. Therefore, the pending claims are not patentable over Bernstein.

29. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BLESSING M. FUBARA whose telephone number is (571)272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Blessing M. Fubara/
Examiner, Art Unit 1618